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Article

Facile Hydrogenative Deprotection of *N*-Benzyl Groups Using a Mixed Catalyst of Palladium and Niobic Acid-on-Carbon

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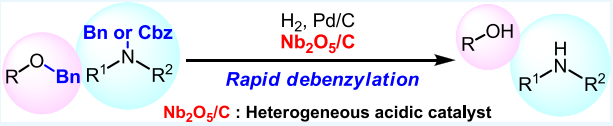
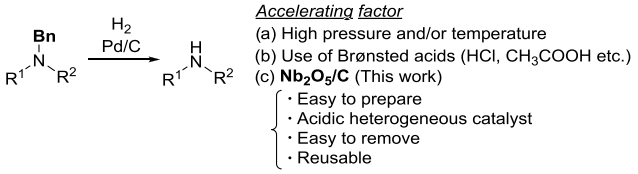
ABSTRACT: The palladium-on-carbon (Pd/C)-catalyzed hydrogenative deprotection of the *N*-benzyl-protecting group was effectively facilitated by the combined use of niobic acid-on-carbon (Nb_2O_5/C). Nb_2O_5/C is an acidic heterogeneous catalyst prepared from $NbCl_5$ and activated carbon. The catalysts were easily removed from the reaction mixture and reusable. Deprotected amines were obtained in excellent yields without an additional neutralization process. The facilitating effect of Nb_2O_5/C was also observed during the Pd/C-catalyzed hydrogenative deprotection of the *N*-benzyloxycarbonyl (Cbz) and *O*-benzyl groups.



INTRODUCTION

Protecting groups are crucially important for the efficient synthesis of the target molecules.[1] The benzyl (Bn) group is often utilized as a protecting group for amine functionalities, and deprotection of the *N*-benzyl-protected amines can be carried out under various reaction conditions in the presence of a Lewis acid (e.g., BBr_3,[2a] BCl_3,[2b] or $AlCl_3$ in anisole[2c]), Brønsted acid [e.g., aqueous H_2SO_4 and[3a] *p*-toluenesulfonic acid (TsOH) in toluene[3b] or trifluoroacetic acid (TFA) in toluene[3c]], or oxidants [e.g., Oxone,[4a] *N*-Iodosuccinimide (NIS),[4b] 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ),[4c] and ammonium cerium(IV) nitrate (CAN)[4d]]. The Pd/C-catalyzed hydrogenation[1] is also often used for deprotection of the *N*-benzyl protecting group as a green sustainable method due to the easy removal and reuse of the catalyst. However, due to the strong coordination ability of amines to Pd, the catalytic activity gradually decreases depending on the extended contact time of the amines (the substrate and product) and Pd. Therefore, high pressure and/or high temperature are often required to complete the deprotection.[5] Although the amine hydrochloride sometimes acted as a relatively slow-acting catalyst poison,[6] the addition of hydrochloric acid or acetic acid for the Pd/C-catalyzed hydrogenative deprotection of the *N*-benzyl protecting group delayed the poisoning rate of Pd/C by the formation of amine salts to facilitate the deprotection.[7] However, a neutralization process was required to isolate the desired debenzylated amine. By the way, niobic acid (Nb_2O_5) possessing properties as both Brønsted and Lewis acids[8] has attracted much attention as an acidic solid catalyst to promote esterification,[9a] amidation,[9b] cyclic imide synthesis,[9c] and dehydration.[9d] Nb_2O_5/C, in which Nb_2O_5 was highly dispersed on the activated carbon, is also utilized in a number of reactions, such as photodegradation,[10a,b] hydrogenation,[10c] and dehydration.[10d,e] We have developed a novel preparation method of Nb_2O_5/C from $NbCl_5$ and its application as an effective cocatalyst for the Pd/C-catalyzed hydrogenative deprotection of the *N*-benzyl protecting group to provide the corresponding debenzylated amine without an additional neutralization process (Scheme 1).

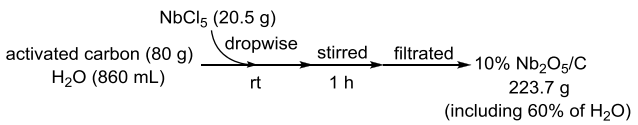
Scheme 1. Pd/C-Catalyzed Hydrogenative Deprotection of *N*-Benzyl groups



RESULTS AND DISCUSSION

Nb_2O_5/C could be easily prepared from commercially available $NbCl_5$ and activated carbon (Scheme 2). To the suspension of activated carbon (80 g) in deionized water (860 mL), the

Scheme 2. Preparation of Nb_2O_5/C



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$NbCl_5$ (20.5 g) was added dropwise at room temperature. [*Caution*: $NbCl_5$ intensely reacted with water along with the evolution of hydrogen chloride (HCl)]. After stirring for 1 h, the reaction mixture was filtered to obtain 10% Nb_2O_5/C [total 223.7 g including water (60%)].

X-ray photoelectron spectroscopy (XPS) spectra of Nb_2O_5/C (Figure 1) showed characteristic peaks of Nb_2O_5.[11] X-ray

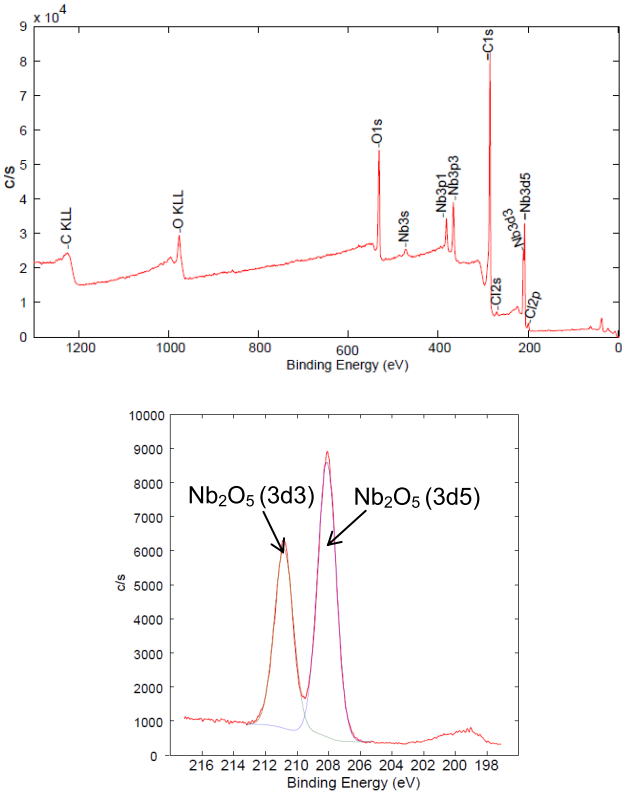

Figure 1. XPS spectra of Nb_2O_5/C.

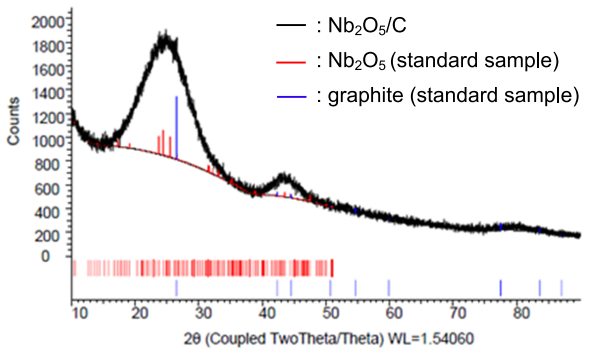

Figure 2. XRD spectrum of Nb_2O_5/C.

diffraction (XRD) analysis (Figure 2) and scanning transmission electron microscopy (STEM) images (Figure 3) of Nb_2O_5/C revealed that Nb_2O_5 was supported in an amorphous form on the activated carbon [the broad peaks (2θ = 22°, 43°) in XRD were derived from carbon, and the peak derived from amorphous Nb_2O_5 was not observed] and well correlated with the literature values.[8,10e] Furthermore, it was identified by electron probe microanalysis (EPMA) that Nb_2O_5 was mainly dispersed on the surface of the activated carbon (Figure S1).

The addition effect of Nb_2O_5/C on the Pd/C-catalyzed deprotection of *N*-benzyl dioctylamine (**1a**; 0.2 mmol) was evaluated at room temperature in MeOH under a hydrogen atmosphere (Figure 4). The deprotection of **1a** partially proceeded by the independent use of 1 mol % of Pd/C to give a mixture of the desired deprotected amine (**2a**, 54%) and recovered **1a** (40%) for 60 min (green line) and the deprotection was still incomplete even after 90 min (turnover frequency: 60 h^{-1}). Meanwhile, the addition of Nb_2O_5/C (1 mol %) efficiently accelerated the Pd/C-catalyzed deprotection of **1a** and the deprotected amine (**2a**) was quantitatively obtained within 45 min (red line; turnover number: 100, turnover frequency: 133 h^{-1}). It is noteworthy that an analytically pure product (**2a**) was isolated by only simple filtration without further purification such as neutralization and/or extraction. Since the reaction never proceeded without Pd/C and **1a** was quantitatively recovered (yellow line), it is obvious that Nb_2O_5/C does not possess a catalyst activity for hydrogenation, but effectively facilitates the Pd/C-catalyzed hydrogenative deprotection of the *N*-benzyl protecting group.

The deprotection of **1a** was also completed in *i*-PrOH instead of MeOH within 45 min (Table 1, entry 2), while toluene and water were inefficient solvents (entries 3 and 4). The 3 mmol scale deprotection of **1a** (1.01 g) was also applicable without any significant loss of the catalytic activity as well (entry 5).

The acceleration effects on the debenzylation of Nb_2O_5/C and other acid catalysts were next compared (Table 2). As noted in Figure 4, the Pd/C-catalyzed hydrogenative deprotection of **1a** in the presence of Nb_2O_5/C as a catalytic additive was completed at room temperature within 45 min (Table 2, entry 1), while the deprotection without Nb_2O_5 was incomplete even after 1 h and the unchanged **1a** was recovered in a 40% yield (entry 3). The dried Nb_2O_5/C was also effective to give **1a** in a quantitative yield for 45 min (entry 2). The use of $Sc(OTf)_3$ (1 mol %), K-10 montmorillonite (10 wt %), AMBERLYST 46 (1 mol %), and phosphotungstic acid (10 wt %) additives all gave unsatisfactory results (entries 3−6). While a remarkable promoting effect was observed in the 1% HCl−MeOH solution as the solvent (entry 7), a significant enhancement of the deprotection was not observed even using a 5% HCl−MeOH solvent (entry 8). These results clearly exhibited the utility of Nb_2O_5/C toward the acceleration of the Pd/C-catalyzed hydrogenative debenzylation.

The scope of substrates for the Pd/C and Nb_2O_5/C-combined debenzylation reaction was next investigated (Table 3). The benzyl-protected *N*-alkylaniline as secondary amines (**1b** and **1c**) smoothly underwent the present hydrogenative deprotection to give the secondary amine derivatives (**2b** and **2c**; entries 1 and 2), and *N*-benzylaniline (**1d**) and *N*,*N*-dibenzylaniline (**1e**) were also effectively deprotected and the corresponding anilines (**2d**) were both obtained in excellent yields (entries 3 and 4). The benzyl-protected primary aliphatic amines (**1f** and **1g**) and cyclic amine (**1h**) were also quantitatively deprotected (entries 5, 7, and 8). While the benzyl amines connected to *N*-heterocycles, such as pyridine (**1i**) and pyrimidine (**1j**), were entirely inactive against the present deprotection reaction conditions (entries 10 and 11), *N*-benzyloxycarbonyl (Cbz)-2-(pyrimidyl)amine (**1k**) was efficiently deprotected to give **2j** in a 97% yield within 1 h (entry 12). The *N*-Cbz-protected dioctylamine (**1l**) was

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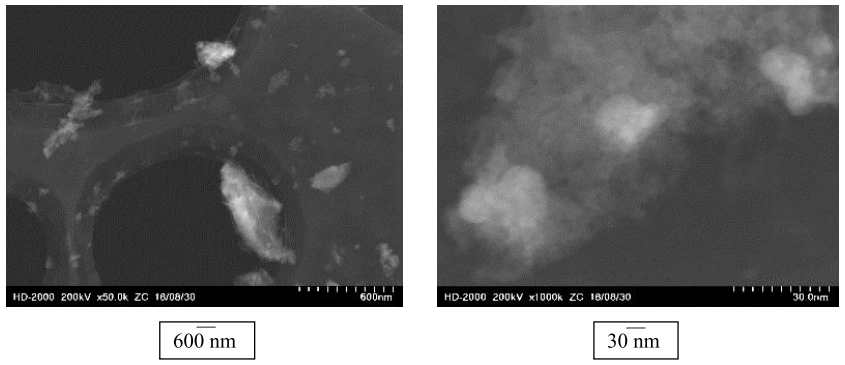


Figure 3. STEM images of Nb_2O_5/C.

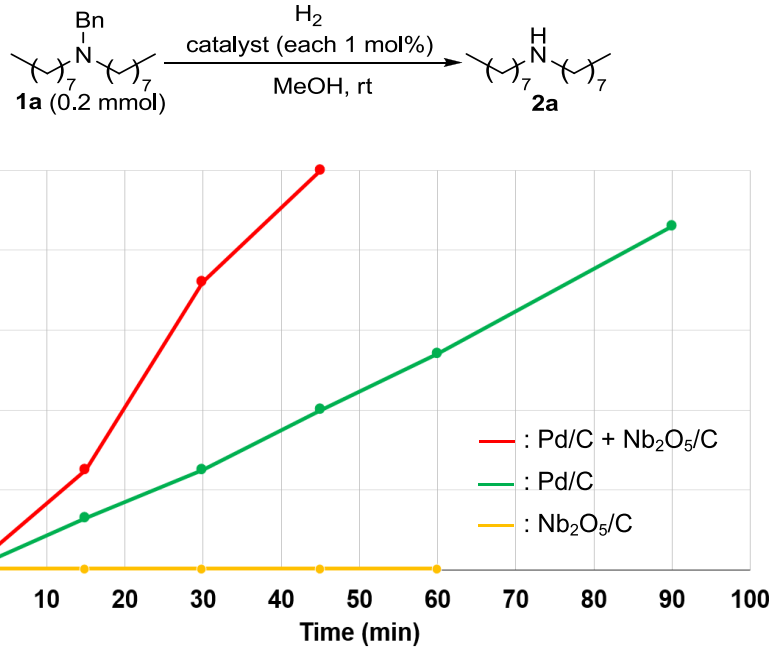
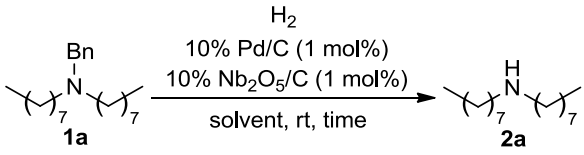


Figure 4. Time-course study of debenzylation using 10% Pd/C and/or 10% Nb_2O_5/C.

Table 1. Solvent Effect



			yield (%)	
entry	solvent	time (min)	1a	2a
1	MeOH	45	0	quant.
2	*i*-PrOH	45	trace	98
3	toluene	60	59	38
4	H_2O	60	98	8
5[a]	MeOH	45	0	99

[a]3 mmol (1.01 g) of **1a** was used.

smoothly converted to **2a** as a secondary aliphatic amine in an excellent yield (entry 14). In addition, the *O*-benzyl-protected phenol (**1m**) and ethylene glycol (**1n**) were also rapidly deprotected using a mixture of Pd/C and Nb_2O_5/C (entries 15 and 17). It is noteworthy that the remarkable accelerating effect of Nb_2O_5/C was observed for all of the Pd/C-catalyzed hydrogenative deprotections of the *N*-Bn-protected amines (**1f** and **1h**) as well as the *N*-Cbz-protected amine (**1k**) and *O*-Bn-protected phenol (**1m**) (entries 5 vs 6, 8 vs 9, 12 vs 13, and 15 vs 16). The present debenzylation of *N*-Bn (**1o**) and *O*-Bn (**1p**) protecting groups could effectively proceed without the cleavage of the coexisting *tert*-butyldimethylsilyl (TBS) ether (entries 18 and 19). The acceleration effect of Nb_2O_5/C was also observed (entries 19 vs 20). The use of HCl as a traditional accelerator[7] caused the deprotection of *O*-Bn as well as *O*-TBS protecting groups (entry 21), which clearly indicated the advantage of the use of Nb_2O_5/C. The mixed catalyst of Pd/C and Nb_2O_5/C was also adaptable to the hydrogenative reduction of alkene, epoxide, aryl chloride, azide, nitro, and benzyl alcohol functionalities to give the corresponding reduced products (Table S1).

The mixture of 10% Pd/C and 10% Nb_2O_5/C could be reused at least three times without any significant loss in the catalytic activity (Table 4). It has also been confirmed that the oxidation state of Nb_2O_5 did not change before and after the reactions (Figure 5; XPS results). It was revealed that palladium as a particle and Nb_2O_5 as an amorphous individually existed after the reaction by STEM images and energy-dispersive X-ray spectrometry (EDS) spectra (Figure 6). Furthermore, the particle size of Pd was found not to be

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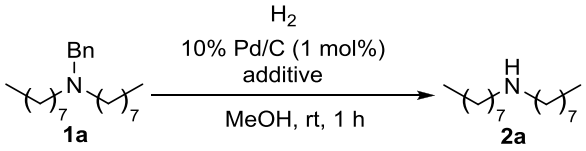
Table 2. Comparison of the Addition Effects of Nb_2O_5/C with Other Acids



		yield (%)	
entry	additive	1a	2a
1[a]	Nb_2O_5/C (1 mol %)	0	quant.
2	Nb_2O_5/C (1 mol %)[d]	0	quant.
3		40	54
4[b]	$Sc(OTf)_3$ (1 mol %)	76	22
5	K-10 montmorillonite (10 wt %)	27	73
6	AMBERLYST 46 (1 mol %)	72	28
7[b]	phosphotungstic acid (10 wt %)	27	66
8[c]	1% HCl−MeOH	13	87
9[c]	5% HCl−MeOH	6	85

[a]For 45 min. [b]The yield was determined by ^{1}H NMR using 1,2-methylenedioxybenzene as an internal standard. [c]The reaction was performed in the HCl−MeOH solution. [d]Nb_2O_5/C was used after washing with MeOH and dried in a desiccator under vacuum overnight.

changed before and after the reaction (Figure S4). Although catalyst activities slightly decreased in the fourth and fifth runs, the acceleration effect was still observed in comparison with the reaction using an independent Pd/C. During the present deprotection, the leaching of Pd (<0.1 ppm) and Nb species (<1.0 ppm) was hardly detected by the inductively coupled plasma optical emission spectroscopy (ICP-OES) analysis and inductively coupled plasma mass spectroscopy (ICP-MS).

CONCLUSIONS

We have newly demonstrated that Nb_2O_5/C significantly facilitated the Pd/C-catalyzed deprotection of the *N*-benzyl protecting groups under a hydrogen atmosphere. Nb_2O_5/C was easily prepared from $NbCl_5$ and activated carbon and removed by simple filtration from the reaction mixture. The deprotected product could be simply isolated without further neutralization or extraction. The *N*-Cbz- and *O*-Bn-protected groups were also smoothly deprotected under the Pd/C and Nb_2O_5/C-combined hydrogenation conditions for a much shorter reaction time in comparison to the deprotection by the single use of Pd/C. Nb_2O_5/C is useful as a heterogeneous and reusable acidic catalyst from the viewpoint of green and process chemistry.

EXPERIMENTAL SECTION

General Information. All commercially available reagents were used without further purification, except AMBERLYST 46. AMBERLYST 46 was washed with H_2O and MeOH and dried in a desiccator under vacuum overnight. Flash column chromatography was performed with Silica Gel 60 N (Kanto Chemical Co., Inc., 63−210 μm spherical, neutral). ^{1}H and ^{13}C NMR spectra were recorded on a JEOL AL 400 or ECZ 400 or ECA 500 spectrometer at room temperature in $CDCl_3$, CD_3OD, or DMSO-d_6 as a solvent and internal standard (^{1}H NMR: δ = 7.26; ^{13}C NMR: δ = 77.0 for $CDCl_3$, ^{1}H NMR: δ = 3.31 for CD_3OD, ^{1}H NMR: δ = 2.54 for DMSO-d_6), with tetramethylsilane as an internal standard. IR spectra were recorded by a Bruker FT-IR α. Electrospray ionization (ESI) high-resolution mass spectra (HRMS) were measured by a Shimadzu hybrid IT-TOF mass spectrometer. The ULVAC-PHI Quantera SXM was used for X-ray photoelectron spectroscopy (XPS). The SPECTRIS X' Pert PRO-MPD was used for X-ray diffraction (XRD). The JEOL JEM-ARM200F or HITACHI HIGH-TECHNOLOGIES HD-2000 was used for scanning transmission electron microscopy (STEM). The JEOL JXA-8100 was used for electron probe microanalysis (EPMA). Pd leaching was analyzed by inductively coupled plasma optical emission spectroscopy (ICP-OES) using iCAP6500 (Thermo Fisher Scientific). Nb leaching was analyzed by inductively coupled plasma mass spectroscopy (ICP-MS) using 7500ce (Agilent Technologies).

Procedures to Prepare the Substrates and Their Spectroscopic Data. *N-Benzyl Dioctylamine (**1a**).* To a suspension of NaH (60% oil suspension, 640 mg, 16 mmol) in dimethylformamide (DMF; 20 mL), dioctylamine (2.4 mL, 8.0 mmol) was added at 0 °C under an argon atmosphere. After stirring for 0.5 h, benzyl chloride (0.46 mL, 4.0 mmol) was added. The reaction mixture was warmed to room temperature and stirred for a further 4.5 h. The reaction mixture was quenched with water and extracted with *n*-hexane/EtOAc = 4:1. The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by silica-gel column chromatography (*n*-hexane/EtOAc = 20:1) to give *N*-benzyl dioctylamine (1.28 g, 3.88 mmol) in a 97% yield. Colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.33−7.20 (m, 5H), 3.53 (s, 2H), 2.38 (t, J = 7.5 Hz, 4H), 1.46−1.43 (m, 4H), 1.30−1.25 (m, 20H), 0.88 (t, J = 7.5 Hz, 6H). Spectroscopic data of ^{1}H NMR were identical to those reported in ref 12.

*N-Benzyl-N-butyl-m-toluidine (**1b**).* To a suspension of NaH (60% oil suspension, 1.0 g, 25 mmol) in DMF (15 mL), *N*-butyl-*m*-toluidine (1.7 mL, 10.2 mmol) was added at 0 °C under an argon atmosphere. After stirring for 10 min, benzyl chloride (1.7 mL, 15 mmol) was added. The reaction mixture was warmed to room temperature and stirred for a further 24 h. The reaction mixture was quenched with water and extracted with *n*-hexane/EtOAc = 4:1. The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by silica-gel column chromatography (*n*-hexane/EtOAc = 10:1) to give *N*-benzyl-*N*-butyl-*m*-toluidine (1.04 g, 4.1 mmol) in a 41% yield. Yellow oil; IR (ATR) cm^{-1}: 3028, 2955, 2927, 2870, 1600, 1579, 1494, 1451, 1354, 1290, 1253, 1177, 1129, 1075, 1027, 988, 949, 836, 762, 729, 691, 615, 458; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32−7.21 (m, 5H), 7.06 (t, J = 3.2 Hz, 1H), 6.49 (m, 3H), 4.53 (s, 2H), 3.36 (t, J = 8.0 Hz, 2H), 2.27 (s, 3H), 1.64 (m, 2H), 1.34 (m, 2H), 0.94 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.91, 139.44, 138.97, 129.19, 128.64, 126.79, 126.70, 117.04, 112.85, 109.48, 54.53, 51.04, 29.43, 22.14, 20.51, 14.14; ESI-HRMS m/z: 254.1980 ([M + H]$^+$); Calcd for $C_{18}H_{23}N$: 254.1903.

*N-Benzyl-N-methylaniline (**1c**).* To a solution of *N*-methylaniline (0.65 mL, 6.0 mmol) and Et_3N (0.55 mL, 4.0 mmol) in MeOH (5 mL), benzyl chloride (0.46 mL, 4.0 mmol) was added at room temperature under an argon atmosphere. After stirring for 16 h, the reaction mixture was concentrated in vacuo. The residue was purified by silica-gel column chromatography (*n*-hexane/EtOAc = 10:1) to give *N*-benzyl-*N*-methylaniline (557 mg, 2.83 mmol) in a 71% yield. Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31 (t, J = 7.5 Hz, 2H), 7.26−7.20 (m, 5 H), 6.75 (d, J = 7.5 Hz, 2H), 6.71 (dd, J

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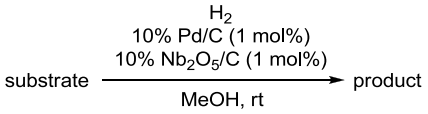
Table 3. Scope of Substrates



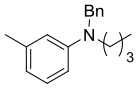
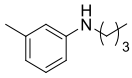
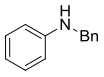
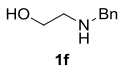
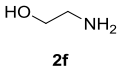
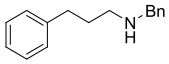
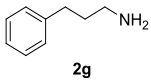
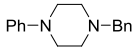
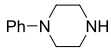
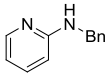
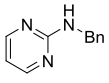
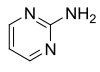
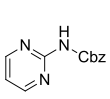
entry	substrate	product	time (h)	yield (%)
1	 **1b**	 **2b**	1	quant.
2	 **1c**	 **2c**	0.5	quant.[a]
3	 **1d**	 **2d**	0.5	quant.[a]
4	 **1e**	**2d**	1	92[a]
5	 **1f**	 **2f**	5.5	quant.[a]
6[b]	**1f**	**2f**	16	quant.[a]
7	 **1g**	 **2g**	10	quant.[a]
8	 **1h**	 **2h**	24	quant.[a]
9[b]	**1h**	**2h**	24	52[a,c]
10	 **1i**	 **2i**	-	no reaction
11	 **1j**	 **2j**	-	no reaction
12	 **1k**	**2j**	1	97
13[b]	**1k**	**2j**	4.5	95

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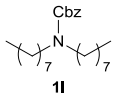
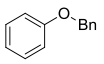
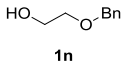
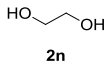
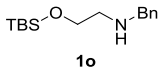
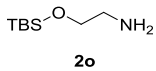
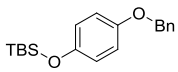
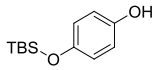
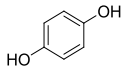
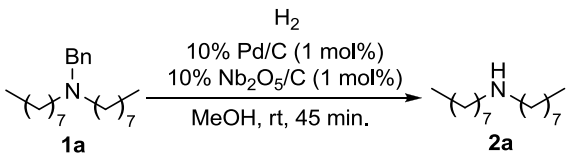
Table 3. continued

entry	substrate	product	time (h)	yield (%)
14	 **1l**	**2a**	0.5	95
15	 **1m**	 **2m**	1.5	94[a]
16[b]	**1m**	**2m**	8	93[a]
17	 **1n**	 **2n**	0.5	quant.[a]
18	 **1o**	 **2o**	12	93[d]
19	 **1p**	 **2p**	1.5	quant.[d]
20[b]	**1p**	**2p**	3	quant.[d]
21[b,e]	**1p**	 **2p'**	1.5	98[d]

[a]Reaction was carried out in CD_3OD, and the yield was determined by ^1H NMR using 1,2-methylenedioxybenzene as an internal standard. [b]Without Nb_2O_5/C. [c]48% of the substrate was recovered. [d]The yield was determined by ^1H NMR using 1,2-methylenedioxybenzene as an internal standard. [e]5% HCl−MeOH solution was used as a solvent.

Table 4. Reuse Test Using the Mixture of Pd/C and Nb_2O_5/C



1a **2a**

	yield (%)	
run	**1a**	**2a**
1st	0	97
2nd	0	97
3rd	0	quant.
4th	14	82
5th	12	85

= 7.5, 7.5 Hz, 1H), 4.54 (s, 2H), 3.02 (s, 3H). Spectroscopic data of ^1H NMR were identical to those reported in ref 13.

*N-Benzyl-3-phenylpropan-1-amine (**1g**).* To a solution of 3-phenylpropan-1-amine (1.0 mL, 7.0 mmol) in MeOH (15 mL), benzaldehyde (0.5 mL, 5.0 mmol) was added at room temperature under an argon atmosphere. After stirring for 1 h, $NaBH_4$ (206 mg, 5.5 mmol) was added. The reaction mixture was stirred for a further 1 h and concentrated in vacuo. The residue was extracted with sat. $NaHCO_3$ aq. and diethyl ether. The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by silica-gel column chromatography (only EtOAc) to give *N*-benzyl-3-phenylpropan-1-amine (1.15 g, 5.1 mmol) in a 72% yield. Colorless oil; ^1H NMR (500 MHz, $CDCl_3$): δ 7.34−7.24 (m, 7H), 7.19−7.17 (m, 3H), 3.78 (s, 2H), 2.67 (m, 4H), 1.84 (m, 2H). Spectroscopic data of ^1H NMR were identical to those reported in ref 14.

*N-Benzyl-4-phenylpiperazine (**1h**).* To a solution of 1-phenylpiperazine (0.76 mL, 5.0 mmol) in EtOAc (10 mL), benzyl chloride (0.57 mL, 5.0 mmol) was added at room temperature under an argon atmosphere. After stirring for 1 h, the reaction mixture was concentrated in vacuo. The residue was purified by silica-gel column chromatography (*n*-hexane/EtOAc = 10:1, then only EtOAc) to give 1-benzyl-4-phenylpiperazine (600 mg, 2.36 mmol) in a 47% yield. Yellow oil; ^1H NMR (500 MHz, $CDCl_3$): δ 7.37−7.24 (m, 7H), 6.92 (d, J = 8.0 Hz, 2H), 6.85 (t, J = 7.5 Hz, 1H), 3.57 (s, 2H), 3.20 (t, J = 5.0 Hz, 4H), 2.61 (t, J = 5.0 Hz, 4H). Spectroscopic data of ^1H NMR were identical to those reported in ref 15.

*N-Benzyl-2-aminopyrimidine (**1j**).* To a suspension of NaOH (24 mg, 0.6 mmol) and 2-aminopyrimidine (290 mg, 3.0 mmol) in toluene (5 mL), benzyl alcohol (0.37 mL, 3.6 mmol) was added at room temperature under an argon atmosphere. The reaction mixture was refluxed at 130 °C for 4.5 h. The reaction mixture was concentrated in vacuo and extracted EtOAc and water. The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by silica-gel column chromatography (*n*-hexane/

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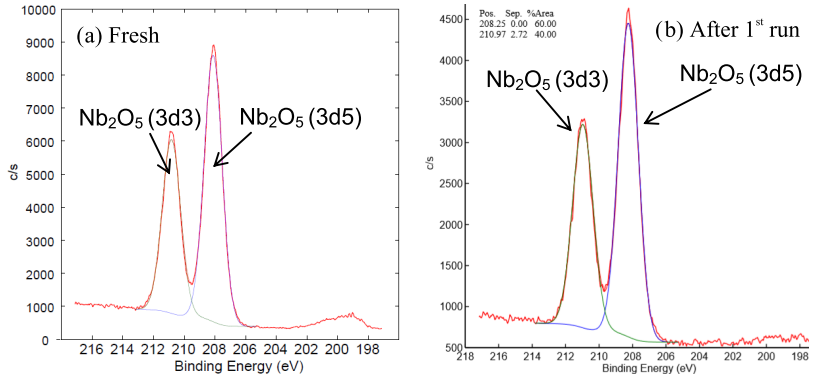

Figure 5. XPS spectra of fresh (a: same as Figure 2) and used (b) Nb_2O_5/C.

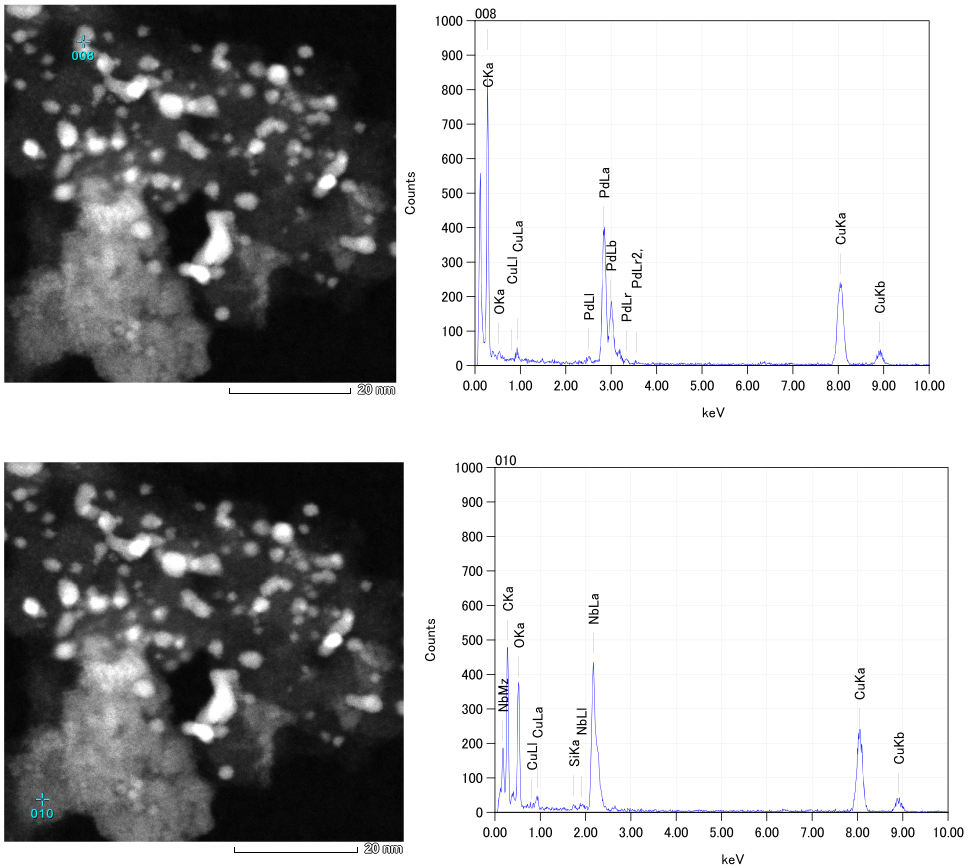

Figure 6. STEM images and EDS spectra of the mixture of used Pd/C and Nb_2O_5/C (Elemental analysis of metals at the light blue "+" mark is shown in the right spectra).

EtOAc = 1:1) to give *N*-benzyl-2-aminopyrimidine (510 mg, 2.77 mmol) in a 91% yield. Colorless solid; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.29 (d, J = 4.8 Hz, 2H), 7.37−7.26 (m, 5H), 6.56 (t, J = 4.8 Hz, 1H), 5.45 (brs, 1H), 4.65 (d, J = 7.0 Hz, 2H). Spectroscopic data of ^{1}H NMR were identical to those reported in ref 16.

*N-Benzyloxycarbonyl-2-aminopyrimidine (**1k**).* To a suspension of 2-aminopyrimidine (480 mg, 5.0 mmol) in H_2O (10 mL), benzyl chloroformate (0.74 mL, 5.0 mmol) was added at room temperature. After stirring for 15 min, 1 mol/L NaOH aq. was added and the suspension was passed through a filter paper. The filtrated solid was washed with *n*-hexane and dried in a desiccator under vacuum overnight to give *N*-benzyloxycarbonyl -2-aminopyrimidine (134 mg, 0.58 mmol) in a 12% yield. Pale yellow solid; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.58 (d, J = 4.5 Hz, 2H), 8.04 (brs, 1H), 7.44 (d, J = 6.5 Hz, 2H), 7.40−7.35 (m, 3H), 6.97 (t, J = 4.5 Hz, 1H), 5.26 (s, 2H). Spectroscopic data of ^{1}H NMR were identical to those reported in ref 17.

*N-Benzyloxycarbonyldioctylamine (**1l**).* To a solution of KOH (210 mg, 3.75 mmol) in H_2O (5 mL) and $CHCl_3$ (5 mL), dioctylamine (0.6 mL, 2.0 mmol) and benzyl chloroformate (0.68 mL, 2.0 mmol) were added at room temperature under an argon atmosphere. The reaction mixture was stirred for 1 h and extracted with diethyl ether. The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by silica-gel column chromatography (*n*-hexane/EtOAc = 20:1) to give *N*-

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benzyloxycarbonyldioctylamine (222 mg, 0.59 mmol) in a 30% yield. Colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.37−7.28 (m, 5H), 5.12 (s, 2H), 3.22 (m, J = 4.8 Hz, 4H), 1.52 (m, 4H), 1.37−1.16 (m, 20H), 0.88 (t, J = 5.6 Hz, 6H). Spectroscopic data of ^{1}H NMR were identical to those reported in ref 18.

*N-Benzyl-2-((tert-butyldimethylsilyl)oxy)ethan-1-amine (**1o**).* To a solution of *N*-benzyl-2-aminoethanol (450 mg, 3 mmol) in CH_2Cl_2 (15 mL), *tert*-butyldimethylchlorosilane (450 mg, 3 mmol) and imidazole (400 mg, 6 mmol) were added at room temperature under an argon atmosphere. The reaction mixture was stirred for 1 h and then quenched with H_2O. The aqueous layer was extracted with CH_2Cl_2. The combined organic layer was dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by silica-gel column chromatography (*n*-hexane/EtOAc = 2:1) to give *N*-benzyl-2-((*tert*-butyldimethylsilyl)oxy)ethan-1-amine (560 mg, 2.11 mmol) in a 71% yield. Colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.33 (d, J = 5.6 Hz, 4H), 7.25−7.21 (m, 1H), 3.82 (s, 2H), 3.74 (t, J = 5.0 Hz, 2H), 2.74 (t, J = 5.0 Hz, 2H), 0.89 (s, 9H), 0.06 (s, 6H). Spectroscopic data of ^{1}H NMR were identical to those reported in ref 19.

*O-(tert-Butyldimethylsilyl)benzyloxyphenol (**1p**).* To a solution of 4-benzyloxyphenol (1.01 g, 5 mmol) in DMF (10 mL), *tert*-butyldimethylchlorosilane (1.51 g, 10 mmol) and imidazole (1.38 g, 20 mmol) were added at room temperature under an argon atmosphere. The reaction mixture was stirred for 3 h and then quenched with sat. $NaHCO_3$ aq. and H_2O. The aqueous layer was extracted with *n*-hexane/EtOAc = 4:1. The combined organic layer was dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by silica-gel column chromatography (*n*-hexane/EtOAc = 10:1) to give *O-tert*-butyldimethylsilyl benzyloxyphenol (1.43 g, 4.53 mmol) in a 90% yield. Colorless solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.44−7.32 (m, 5H), 6.86−6.82 (m, 2H), 6.77−6.75 (m, 2H), 5.00 (s, 2H), 0.97 (s, 9H), 0.17 (s, 6H). Spectroscopic data of ^{1}H NMR were identical to those reported in ref 20.

Typical Procedures in Pd/C- and Nb_2O_5/C-Catalyzed Hydrogenative Deprotection. *Typical Procedure A.* 10% Pd/C (2.1 mg, 0.002 mmol) or a mixture of 10% Pd/C and 10% Nb_2O_5/C (including 60% water, 17.3 mg, 0.002 mmol) was added to a solution of benzyl- or Cbz-protected substrate (**1**: 0.2 mmol) in MeOH (1 mL). The inside air was replaced with H_2 (balloon) by three vacuum/H_2 cycles. The reaction mixture was stirred at room temperature until the thin layer chromatography (TLC) monitoring indicated the complete consumption of the starting material. Then, the reaction mixture was passed through a Celite pad or membrane filter using EtOAc to remove Pd/C and Nb_2O_5/C. The filtrate was concentrated in vacuo to give deprotected product (**2**).

Typical Procedure B. 10% Pd/C (2.1 mg, 0.002 mmol) or a mixture of 10% Pd/C and 10% Nb_2O_5/C (including 60% water, 17.3 mg, 0.002 mmol) was added to a solution of benzyl- or Cbz-protected substrate (**1**: 0.2 mmol) in CD_3OD (1 mL). The inside air was replaced with H_2 (balloon) by three vacuum/H_2 cycles. The reaction mixture was stirred at room temperature until the TLC monitoring indicated the complete consumption of the starting material. Then, 1,2-methylenedioxybenzene was added as an internal standard and the reaction mixture was passed through a membrane filter to remove Pd/C and Nb_2O_5/C. The yield of **2** was determined by ^{1}H NMR using 1,2-methylenedioxybenzene (20.5 μL, 0.2 mmol) as an internal standard.

Spectroscopic Data of the Deprotected Products. The yield of the product possessing the low boiling point was determined by ^{1}H NMR using 1,2-methylenedioxybenzene as an internal standard in CD_3OD. Toluene is also partially detected as a byproduct in deprotection (see the spectra in Supporting Information).

*Dioctylamine (**2a**) in Figure 4, Table 1, Table 2, Table 4, and Table 3, Entry 14.* When using **1a** (66.7 mg, 0.2 mmol) according to method A, dioctylamine (**2a**: 48.7 mg, 0.2 mmol) was obtained for 0.75 h in a quantitative yield without further column chromatography purification. When using **1l** (75.3 mg, 0.2 mmol) according to method A, dioctylamine (**2a**: 45.4 mg, 0.188 mmol) was obtained for 0.5 h in a 94% yield without further column chromatography purification. Colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.58 (t, J = 5.6 Hz, 4H), 1.48 (t, J = 5.6 Hz, 4H), 1.31−1.27 (m, 20H), 0.88 (t, J = 5.2 Hz, 6H). Spectroscopic data of ^{1}H NMR were identical to those reported in ref 21.

*N-Butyl-m-toluidine (**2b**) in Table 3, Entry 1.* When using **1b** (50.5 mg, 0.2 mmol) according to method A, *N*-butyl-*m*-toluidine (**2b**: 33.8 mg, 0.2 mmol) was obtained for 1 h in a quantitative yield without further column chromatography purification. Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.06 (t, J = 8.8 Hz, 1H), 6.51 (t, J = 7.6 Hz, 1H), 6.43−6.41 (m, 2H), 3.77 (brs, 1H), 3.10 (t, J = 7.2 Hz, 2H), 2.27 (s, 3H), 1.59 (m, 2H), 1.42 (m, 2H), 0.95 (t, J = 8.0 Hz, 3H). Spectroscopic data of ^{1}H NMR were identical to those reported in ref 22.

*N-Methylaniline (**2c**) in Table 3, Entry 2.* When using **1c** (39.3 mg, 0.2 mmol) according to method B, *N*-methylaniline (**2c**: 0.2 mmol) was obtained for 0.5 h in a quantitative yield. ^{1}H NMR (400 MHz, CD_3OD): δ 7.11 (t, J = 8.0 Hz, 2H), 6.63−6.60 (m, 3H), 2.75 (s, 3H). Spectroscopic data of ^{1}H NMR of the product were identical to those of the commercially available authentic sample.

*Aniline (**2d**) in Table 3, Entries 3 and 4.* When using **1d** (36.7 mg, 0.2 mmol) according to method B, aniline (**2d**: 0.2 mmol) was obtained for 0.5 h in a quantitative yield without further column chromatography purification. When using **1e** (44.6 mg, 0.2 mmol) according to method B, aniline (**2d**: 0.184 mmol) was obtained for 1 h in a 92% yield. ^{1}H NMR (400 MHz, CD_3OD): δ 7.07 (t, J = 8.4 Hz, 2H), 6.73−6.65 (m, 3H). Spectroscopic data of ^{1}H NMR of the product were identical to those of the commercially available authentic sample.

*2-Aminoethanol (**2f**) in Table 3, Entries 5 and 6.* When using **1f** (30.4 mg, 0.2 mmol) according to method B, 2-aminoethanol (**2f**: 0.2 mmol) was obtained for 5.5 h in a quantitative yield. ^{1}H NMR (400 MHz, CD_3OD):δ 3.56 (t, J = 4.4 Hz, 2H), 2.71 (t, J = 4.4 Hz, 2H). Spectroscopic data of ^{1}H NMR of the product were identical to those of the commercially available authentic sample.

*3-Phenylpropan-1-amine (**2g**) in Table 3, Entry 7.* When using **1g** (44.9 mg, 0.2 mmol) according to method B, 3-phenylpropan-1-amine (**2g**: 0.2 mmol) was obtained for 10 h in a quantitative yield. ^{1}H NMR (400 MHz, CD_3OD): δ 7.27−7.13 (m, 5H), 2.66−2.62 (m, 4H), 1.81−1.73 (m, 2H). Spectroscopic data of ^{1}H NMR of the product were identical to those of the commercially available authentic sample.

*1-Phenylpiperazine (**2h**) in Table 3, Entries 8 and 9.* When using **1h** (50.9 mg, 0.2 mmol) according to method B, 1-phenylpiperazine (**2h**: 0.2 mmol) was obtained for 24 h in a quantitative yield. ^{1}H NMR (400 MHz, CD_3OD): δ 7.24 (m,

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2H), 6.97 (d, J = 6.4 Hz, 2H), 6.85 (t, J = 6.4 Hz, 1H), 3.12 (t, J = 5.6 Hz, 4H), 2.97 (t, J = 5.6 Hz, 4H). Spectroscopic data of ^{1}H NMR of the product were identical to those of the commercially available authentic sample.

*2-Aminopyrimidine (**2j**) in Table 3, Entries 12 and 13.* When using **1k** (45.4 mg, 0.2 mmol) according to method A, 2-aminopyrimidine (**2j**: 18.2 mg, 0.19 mmol) was obtained for 1 h in a 95% yield without further column chromatography purification. White solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.30 (d, J = 5.0 Hz, 2H), 6.63 (dd, J = 5.0, 5.0 Hz, 1H), 5.07 (brs, 2H). Spectroscopic data of ^{1}H NMR were identical to those reported in ref 23.

*Phenol (**2m**) in Table 3, Entries 15 and 16.* When using **1m** (37.1 mg, 0.2 mmol) according to method B, phenol (**2m**: 0.2 mmol) was obtained for 1.5 h in a 94% yield. ^{1}H NMR (400 MHz, CD_3OD): δ 7.18−7.13 (m, 2H), 6.81−6.74 (m, 3H). Spectroscopic data of ^{1}H NMR of the product were identical to those of the commercially available authentic sample.

*Ethylene Glycol (**2n**) in Table 3, Entry 17.* When using **1n** (30.3 mg, 0.2 mmol) according to method B, ethylene glycol (**2n**: 0.2 mmol) was obtained for 0.5 h in a quantitative yield. ^{1}H NMR (400 MHz, CD_3OD): δ 4.00 (s, 4H). Spectroscopic data of ^{1}H NMR of the product were identical to those of the commercially available authentic sample.

*2-Amino-1-(tert-butyldimethylsilyloxy)ethanol (**2o**) in Table 3, Entry 18.* 10% Pd/C (2.1 mg, 0.002 mmol) and 10% Nb_2O_5/C (5.3 mg, 0.002 mmol) were added to a solution of **1o** (53 mg, 0.2 mmol) in MeOH (1 mL). The inside air was replaced with H_2 (balloon) by three vacuum/H_2 cycles. The reaction mixture was stirred at room temperature for 12 h. Then, the reaction mixture was passed through a membrane filter using diethyl ether to remove Pd/C and Nb_2O_5/C. The filtrate was concentrated in vacuo to give 2-amino-1-(*tert*-butyldimethylsilyloxy)ethanol (**2o**, 0.185 mmol) in a 93% yield. The yield was determined by ^{1}H NMR using 1,2-methylenedioxybenzene (20.5 μL, 0.2 mmol) as an internal standard. Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.62 (t, J = 4.8 Hz, 2H), 2.76 (t, J = 4.8 Hz, 2H), 0.89 (s, 9H), 0.06 (s, 6H). Spectroscopic data of ^{1}H NMR were identical to those reported in ref 24.

*4-(tert-Butyldimethylsilyloxy)phenol (**2p**) in Table 3, Entries 19 and 20.* When using **1p** (63.0 mg, 0.2 mmol) according to method A, 4-(*tert*-butyldimethylsilyloxy) phenol (**2p**: 45.5 mg, 0.2 mmol) was obtained for 1.5 h in a quantitative yield. Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.73−6.69 (m, 4H), 5.02 (brs, 1H), 0.99 (s, 9H), 0.17 (s, 6H). Spectroscopic data of ^{1}H NMR were identical to those reported in ref 25.

*Hydroquinone (**2p′**) in Table 3, Entry 21.* 10% Pd/C (2.1 mg, 0.002 mmol) and 10% Nb_2O_5/C (5.3 mg, 0.002 mmol) were added to a solution of **1p** (63.0 mg. 0.2 mmol) in 5% HCl−MeOH (1 mL). The inside air was replaced with H_2 (balloon) by three vacuum/H_2 cycles. The reaction mixture was stirred at room temperature for 1.5 h. Then, the reaction mixture was passed through a membrane filter using EtOAc to remove Pd/C and the filtrate was washed with 50% $NaHCO_3$ aq. The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo to give hydroquinone (**2p′**, 0.196 mmol) in a 98% yield. The yield was determined by ^{1}H NMR using 1,2-methylenedioxybenzene (20.5 μL, 0.2 mmol) as an internal standard. White solid; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.61 (brs, 2H), 6.54 (s, 4H). Spectroscopic data of ^{1}H NMR were identical to those reported in ref 26.

Scale-up. The mixture of 10% Pd/C and 10% Nb_2O_5/C (including 60% water, 262 mg, 0.03 mmol) was added to a solution of *N*-benzyl dioctylamine (**1a**: 1.0 g, 3.02 mmol) in MeOH (15 mL). The inside air was replaced with H_2 (balloon) by three vacuum/H_2 cycles. The reaction mixture was stirred at room temperature for 45 min. Then, the reaction mixture was passed through a filter paper using EtOAc to remove Pd/C and Nb_2O_5/C. The filtrate was concentrated in vacuo to give dioctylamine (**2a**: 724 mg, 2.99 mmol) in a 99% yield.

Reuse Test. To a solution of *N*-benzyl dioctylamine (**1a**: 0.2 mmol) in MeOH (1 mL), the mixture of 10% Pd/C and 10% Nb_2O_5/C (7.4 mg, 0.002 mmol) was added. The inside air was replaced with H_2 (balloon) by three vacuum/H_2 cycles. The reaction mixture was stirred at room temperature until the TLC monitoring indicated the complete consumption of the starting material. The reaction mixture was passed through a filter paper and the catalyst was washed with EtOAc. The filtrate was concentrated in vacuo. The filtrated catalysts were further washed with MeOH and water and dried in a desiccator under vacuum overnight, then the recovered catalyst was used for the next run. The results of the reuse test are summarized in Table 4.

Metal Leaching Test. 10% Pd/C (42.6 mg, 0.04 mmol) and 10% Nb_2O_5/C (106.3 mg, 0.04 mmol) were added to a solution of *N*-benzyl dioctylamine (**1a**: 1.33 g, 4.0 mmol) in MeOH (20 mL). The inside air was replaced with H_2 (balloon) by three vacuum/H_2 cycles. The reaction mixture was stirred at room temperature for 45 min. Then, the reaction mixture was passed through a Celite pad using MeOH (50 mL) to remove Pd/C and Nb_2O_5/C. The residue was diluted with MeOH to 100 mL. Pd leaching was analyzed by inductively coupled plasma optical emission spectroscopy (ICP-OES). The Nb leaching was analyzed by inductively coupled plasma mass spectroscopy (ICP-MS). Pd species (<0.1 ppm) and Nb species (<1.0 ppm) were hardly detected.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.9b03226.

EPMA spectrum of Nb_2O_5/C, XPS spectra, and STEM images of Pd/C; XRD spectra are also indicated; details of hydrogenative reduction and spectroscopic data of substrates and products (PDF)

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Notes

The authors declare no competing financial interest.

REFERENCES

(1) Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 4th ed.; John Wiley & Sons, Inc: New Jersey, 2014.
(2) (a) Paliakov, E.; Strekowski, L. Boron tribromide mediated debenzylation of benzylamino and benzyloxy groups. *Tetrahedron Lett.* **2004**, *45*, 4093−4095. (b) Okano, K.; Okuyama, K.; Fukuyama, T.; Tokuyama, H. Mild Debenzylation of Aryl Benzyl Ether with BCl_3 in the Presence of Pentamethylbenzene as a Non-Lewis-Basic Cation Scavenger. *Synlett* **2008**, *13*, 1977−1980. (c) Watanabe, T.; Kobayashi, A.; Nishiura, M.; Takahashi, H.; Usui, T.; Kamiyama, I.; Mochizuki, N.; Noritake, K.; Yokoyama, Y.; Murakami, Y. Synthetic Studies on Indoles and Related Compounds. XXVI. The Debenzylation of Protected Indole Nitrogen with Aluminum Chloride. *Chem. Pharm. Bull.* **1991**, *39*, 1152−1156.
(3) (a) Kowalski, P.; Majka, Z.; Kowalska, T. Acid-catalyzed *N*-debenzylation of Benzylaminopyridines. *Chem. Heterocycl. Compd.* **1998**, *34*, 740−741. (b) Chern, C.; Huang, Y.; Kan, W. M. Selective *N*-debenzylation of amides with *p*-TsOH. *Tetrahedron Lett.* **2003**, *44*, 1039−1041. (c) Fletcher, S.; Gunning, P. T. Mild, efficient and rapid *O*-debenzylation of ortho-substituted phenols with trifluoroacetic acid. *Tetrahedron Lett.* **2008**, *49*, 4817−4819.
(4) (a) Moriyama, K.; Nakamura, Y.; Togo, H. Oxidative Debenzylation of *N*-Benzyl Amides and O-Benzyl Ethers Using Alkali Metal Bromide. *Org. Lett.* **2014**, *16*, 3812−3815. (b) Grayson, E. J.; Daxis, B. G. A Tuneable Method for *N*-Debenzylation of Benzylamino Alcohols. *Org. Lett.* **2005**, *7*, 2361−2364. (c) Baek, S.; Jo, H.; Kim, H.; Kim, H.; Kim, S.; Kim, D. Highly Stereoselective and Efficient Total Synthesis of (+)-Laurencin. *Org Lett.* **2005**, *7*, 75−77. (d) Bull, S. D.; Davis, S. G.; Fenton, G.; Mulvaney, A. W.; Prasad, R. S.; Smith, A. D. Chemoselective debenzylation of *N*-benzyl tertiary amines with ceric ammonium nitrate. *J. Chem. Soc., Perkin Trans. 1* **2000**, *1*, 3765−3774.
(5) (a) Kanai, M.; Yasumoto, M.; Kuriyama, Y.; Inomiya, K.; Katsuhara, Y.; Higashiyama, K.; Ishii, A. Practical Synthesis of Optically Active Fluorine-substituted α-Phenylethylamines by Retardation of Hydrogenolytic Cleavage at Benzylic Position. *Chem. Lett.* **2004**, *33*, 1424−1425. (b) Pallenberg, A. J. A new and simplified method for hydrogenolytic deprotection in solution-phase peptide synthesis. *Tetrahedron Lett.* **1992**, *33*, 7693−7696. (c) Romanens, A.; Belamger, G. Preparation of Conformationally Restricted $\beta^{2,2}$- and $\beta^{2,2,3}$-Amino Esters and Derivatives Containing an All-Carbon Quaternary Center. *Org. Lett.* **2015**, *17*, 322−325.
(6) (a) Sajiki, H.; Kume, A.; Hattori, K.; Hirota, K. Mild and general procedure for Pd/C-catalyzed hydrodechlorination of aromatic chlorides. *Tetrahedron Lett.* **2002**, *43*, 7247−7250. (b) Sajiki, H.; Kume, A.; Hattori, K.; Nagase, H.; Hirota, K. Complete and truly catalytic degradation method of PCBs using Pd/C−Et_3N system under ambient pressure and temperature. *Tetrahedron Lett.* **2002**, *43*, 7251−7254. (c) Monguchi, Y.; Kume, A.; Hattori, K.; Maegawa, T.; Sajiki, H. Pd/C−Et_3N-mediated catalytic hydrodechlorination of aromatic chlorides under mild conditions. *Tetrahedron* **2006**, *62*, 7926−7933. (d) Monguchi, Y.; Kume, A.; Sajiki, H. Facile and catalytic degradation method of DDT using Pd/C−Et_3N system under ambient pressure and temperature. *Tetrahedron* **2006**, *62*, 8384−8392.
(7) (a) Vannice, M. A.; David, A. Control of catalytic debenzylation and dehalogenation reactions during liquid-phase reduction by H_2. *J. Catal.* **2006**, *237*, 349−358. (b) Studer, M.; Blaser, H. Influence of catalyst type, solvent, acid and base on the selectivity and rate in the catalytic debenzylation of 4-chloro-*N*,*N*-dibenzyl aniline with Pd/C and H_2. *J. Mol. Catal. A: Chem.* **1996**, *112*, 437−445. (c) Glase, S. A.; Corbin, A. E.; Pugsley, T. A.; Heffner, T. G.; Wise, L. D. Synthesis and dopaminergic activity of pyridine analogs of 5-hydroxy-2-(di-n-propylamino)tetralin. *J. Med. Chem.* **1995**, *38*, 3132−3137. (d) Cheng, C.; Sun, J.; Xing, L.; Xu, J.; Wang, X.; Hu, Y. Highly Chemoselective Pd−C Catalytic Hydrodechlorination Leading to the Highly Efficient *N*-Debenzylation of Benzylamines. *J. Org. Chem.* **2009**, *74*, 5671−5674. (e) Santarem, M.; Vanucci-Bacque, C.; Lhommet, G. Formal Total Synthesis of (+)-Gephyrotoxin. *J. Org. Chem.* **2008**, *73*, 6466−6469.
(8) Nakajima, K.; Baba, Y.; Noma, R.; Kitano, M.; Kondo, J. N.; Hayashi, S.; Hara, M. $Nb_2O_5{\cdot}nH_2O$ as a Heterogeneous Catalyst with Water-Tolerant Lewis Acid Sites. *J. Am. Chem.* **2011**, *133*, 4224−4227.
(9) (a) Rade, L. L.; Lemos, C. O. T.; Barrozo, M. A. S.; Ribas, R. M.; Monteiro, R. S.; Hori, C. E. Optimization of continuous esterification of oleic acid with ethanol over niobic acid. *Renewable Energy* **2018**, *115*, 208−216. (b) Ali, M. A.; Siddiki, S. M. A. H.; Onodera, W.; Kon, K.; Shimizu, K. Amidation of Carboxylic Acids with Amines by Nb_2O_5 as a Reusable Lewis Acid Catalyst. *ChemCatChem* **2015**, *7*, 3555−3561. (c) Ali, M. A.; Moromi, S. K.; Touchy, A.; Shimizu, K. Direct Synthesis of Cyclic Imides from Carboxylic Anhydrides and Amines by Nb_2O_5 as a Water-Tolerant Lewis Acid Catalyst. *ChemCatChem* **2016**, *8*, 891−894. (d) Catrinck Mariana, N.; Ribeiro, E. S.; Monteiro, R. S.; Ribas, R. M.; Barbosa, M. H. P.; Teofilo, R. F. Direct conversion of glucose to 5-hydroxymethylfurfural using a mixture of niobic acid and niobium phosphate as a solid acid catalyst. *Fuel* **2017**, *210*, 67−74.
(10) (a) Karuppuchamy, S.; Matsui, H.; Kira, K.; Haasan, M. A.; Yoshihara, M. Visible light induced photocatalytic activity of Nb_2O_5/carbon cluster/Cr_2O_3 composite materials. *Ceram. Int.* **2012**, *38*, 1515−1521. (b) de Moraes, N. P.; Bacani, R.; Silva, M. L. C. P.; Campos, T. M. B.; Thim, G. P.; Rodrigues, L. A. Effect of Nb/C ratio in the morphological, structural, optical and photocatalytic properties of novel and inexpensive Nb_2O_5/carbon xerogel composites. *Ceram, Int.* **2018**, *44*, 6645−6652. (c) Ye, F.; Zhang, D.; Xue, T.; Wang, Y.; Guan, Y. Enhanced hydrogenation of ethyl levulinate by Pd−AC doped with Nb_2O_5. *Green Chem.* **2014**, *16*, 3951−3957. (d) Karpiński, Z.; Bonarowska, M.; Lomot, D.; Srebowata, A.; Costa, P.; Rodrigues, J. A. Hydrogenolysis of carbon−halogen and carbon−carbon bonds over Pd/Nb_2O_5−Al_2O_3 catalysts. *Catal. Commun.* **2009**, *10*, 1757−1761. (e) Xiong, H.; Wang, T.; Shanks, B. H.; Datye, A. K. Tuning the Location of Niobia/Carbon Composites in a Biphasic Reaction: Dehydration of d-Glucose to 5-Hydroxymethylfurfural. *Catal. Lett.* **2013**, *143*, 509−516.
(11) (a) Thompson, A. C. *X-ray Data Booklet*; Lawrence Berkley National Laboratory: Berkley, 2009. (b) Justin, P.; Charan, P. H. K.; Rao, G. R. High performance Pt−Nb_2O_5/C electrocatalysts for methanol electrooxidation in acidic media. *Appl. Catal., B* **2010**, *100*, 510−515.
(12) Barham, J. P.; John, M. P.; Murphy, J. A. Contra-thermodynamic Hydrogen Atom Abstraction in the Selective C−H Functionalization of Trialkylamine N-CH_3 Groups. *J. Am. Chem. Soc.* **2016**, *138*, 15482−15487.
(13) Barker, T. J.; Jarvo, E. R. Umpolung Amination: Nickel-Catalyzed Coupling Reactions of *N*,*N*-Dialkyl-*N*-chloroamines with Diorganozinc Reagents. *J. Am. Chem. Soc.* **2009**, *131*, 15598−15599.
(14) McGonagle, F. I.; MacMillan, D. S.; Murray, J.; Sneddon, H. F.; Jamiesona, C.; Watson, A. J. B. Development of a solvent selection guide for aldehyde-based direct reductive amination processes. *Green Chem.* **2013**, *15*, 1159−1165.

(15) Murugesh, V.; Bruneau, C.; Achard, M.; Sahoo, A. R.; Sharma, G. V. M.; Suresh, S. Ruthenium catalyzed β-C(sp^3)−H functionalization on the 'privileged' piperazine nucleus. *Chem. Commun.* **2017**, *53*, 10448−10451.
(16) Yu, X.; Liu, C.; Jiang, L.; Xu, Q. Manganese Dioxide Catalyzed *N*-Alkylation of Sulfonamides and Amines with Alcohols under Air. *Org. Lett.* **2011**, *13*, 6184−6187.
(17) Gondi, S. R.; Son, D. Y. Synthesis of (Hetaryl)alkylamines from the Reactions of 2-Aminopyrimidine, 2-Aminothiazole, and 2-Aminothiazoline with Benzyl Bromide and Xylylene Dibromides. *Synth. Commun.* **2008**, *38*, 401−410.
(18) Behloul, C.; Guijarro, D.; Yus, M. Deallyloxy- and debenzyloxycarbonylation of protected alcohols, amines and thiols via a naphthalene-catalysed lithiation reaction. *Tetrahedron* **2005**, *61*, 9319−9324.
(19) Hansen, C. L.; Ohm, R. G.; Olsen, L. B.; Ascic, E.; Tanner, D.; Nielsen, T. E. Catalytic Enantioselective Synthesis of Tetrahydocarbazoles and Exocyclic Pictet−Spengler-Type Reactions. *Org. Lett.* **2016**, *18*, 5990−5993.
(20) McKerlie, F.; Rudkin, I. M.; Wynne, G.; Procter, D. J. Evaluation of a new linker system cleaved using samarium(II) iodide. Application in the solid phase synthesis of carbonyl compounds. *Org. Biomol. Chem.* **2005**, *3*, 2805−2816.
(21) Fukumoto, Y.; Asai, H.; Shimizu, M.; Chatani, N. Anti-Markovnikov Addition of Both Primary and Secondary Amines to Terminal Alkynes Catalyzed by the $TpRh(C_2H_4)_2/PPh_3$ System. *J. Am. Chem. Soc.* **2007**, *129*, 13792−13793.
(22) Byun, E.; Hong, B.; De Castro, K. A.; Lim, M.; Rhee, H. One-Pot Reductive Mono-N-alkylation of Aniline and Nitroarene Derivatives Using Aldehydes. *J. Org. Chem.* **2007**, *72*, 9815−9817.
(23) Elmkaddem, M. K.; Fischmeister, C.; Thomas, C. M.; Renaud, J. Efficient synthesis of aminopyridine derivatives by copper catalyzed amination reactions. *Chem. Commun.* **2010**, *46*, 925−927.
(24) Hoffmann, J.; Kazmaier, U. A Straightforward Approach towards Cyclic Photoactivatable Tubulysin Derivatives. *Angew. Chem., Int. Ed.* **2014**, *53*, 11356−11360.
(25) Kahl, P.; Tkachenko, B. A.; Novikovsky, A. A.; Becker, J.; Dahl, J. E. P.; Carlson, R. M. K.; Fokin, A. A.; Schreiner, P. R. Efficient Preparation of Apically Substituted Diamondoid Derivatives. *Synthesis* **2014**, *46*, 787−798.
(26) Chen, S.; Hossain, M. S.; Foss, F. W. Organocatalytic Dakin Oxidation by Nucleophilic Flavin Catalysts. *Org. Lett.* **2012**, *14*, 2806−2809.

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